General

Guideline Title

American Gastroenterological Association Institute guidelines for the diagnosis and management of acute liver failure.

Bibliographic Source(s)

Flamm SL, Yang YX, Singh S, Falck-Ytter YT, AGA Institute Clinical Guidelines Committee. American Gastroenterological Association Institute guidelines for the diagnosis and management of acute liver failure. Gastroenterology. 2017 Feb;152(3):644-7. [4 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

NEATS Assessment

National Guideline Clearinghouse (NGC) has assessed this guideline's adherence to standards of trustworthiness, derived from the Institute of Medicine's report Clinical Practice Guidelines We Can Trust.

▮▯▯▯▯= Poor   ▮▮▯▯▯= Fair   ▮▮▮▯▯= Good   ▮▮▮▮▯= Very Good   ▮▮▮▮▮= Excellent

Assessment	Standard of Trustworthiness
NO	Disclosure of Guideline Funding Source
▮▮▮▯▯	Disclosure and Management of Financial Conflict of Interests
	Guideline Development Group Composition
UNKNOWN	Multidisciplinary Group
YES	Methodologist Involvement

	Patient and Public Perspectives
	Use of a Systematic Review of Evidence
	Search Strategy
	Study Selection
	Synthesis of Evidence
	Evidence Foundations for and Rating Strength of Recommendations
	Grading the Quality or Strength of Evidence
	Benefits and Harms of Recommendations
	Evidence Summary Supporting Recommendations
	Rating the Strength of Recommendations
	Specific and Unambiguous Articulation of Recommendations
	External Review
	Updating

Recommendations

Major Recommendations

Definitions for the quality of evidence (High, Moderate, Low, Very low) and strength of recommendation (Strong, Conditional) are provided at the end of the "Major Recommendations" field.

Recommendation 1: In patients presenting with acute liver failure, the American Gastroenterological Association (AGA) Institute suggests against routinely testing all patients for Wilson's disease. (Conditional recommendation; very-low-quality evidence)

Comments: In a setting of high clinical suspicion, testing for Wilson's disease can be considered, keeping in mind the low positive predictive value. Although the management and outcome of acute liver failure (ALF) would not be altered, identification of Wilson's disease would allow appropriate post-transplantation management and screening of the patient's family members.

Recommendation 2: In patients presenting with ALF, the AGA suggests testing for herpes simplex virus and treatment of patients with herpes simplex virus. (Conditional recommendation; very-low-quality evidence)

Recommendation 3: In immunocompetent patients presenting with ALF, the AGA suggests against routinely testing all patients for varicella zoster virus (VZV). (Conditional recommendation; very-low-quality evidence)

Recommendation 4: In pregnant women presenting with ALF, the AGA suggests testing for hepatitis E.

(Conditional recommendation; very-low-quality evidence)

Recommendation 5: In patients presenting with ALF, the AGA suggests using Model for End-Stage Liver Disease (MELD) score rather than Kings College Criteria (KCC) as a prognostic scoring system. (Conditional recommendation; very-low-quality evidence)

Comment: A MELD score of 30.5 (fixed cut-off value) should be used for prognosis. Higher scores predict a need for liver transplantation.

Recommendation 6: In patients presenting with ALF, the AGA suggests against the routine use of liver biopsy. (Conditional recommendation; very-low-quality evidence)

Recommendation 7: In patients presenting with ALF, the AGA suggests autoantibody testing be performed. (Conditional recommendation; very-low-quality evidence)

Recommendation 8: In patients presenting with ALF, the AGA suggests against the empiric use of treatments to reduce intracranial pressure (ICP). (Conditional recommendation; very-low-quality evidence)

Recommendation 9: In patients presenting with ALF, the AGA recommends that extracorporeal artificial liver support systems only be used within the context of a clinical trial. (No recommendation)

Recommendation 10: In patients presenting with acetaminophen-associated ALF, the AGA recommends the use of N-acetyl cysteine in acetaminophen-associated ALF. (Strong recommendation; very-low-quality evidence)

Recommendation 11: In patients presenting with non–acetaminophen-associated ALF, the AGA recommends that N-acetyl cysteine be used only in the context of clinical trials. (No recommendation)

Definitions

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Definitions of Quality/Certainty of the Evidence

High	The Committee is very confident that the true effect lies close to that of the estimate of the effect.
Moderate	The Committee is moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	The Committee's confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low	The Committee has very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

GRADE Categories on Strength of Recommendation

	Wording in Guideline	For the Patient	For the Clinician
Strong	"The AGA recommends..."	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.
Conditional	"The AGA suggests..."	The majority of individuals in this situation would want the suggested course of action, but	Different choices will be appropriate for different patients. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients

	Wording in Guideline	For the Patient	For the Clinician
		many would not.	when working towards a decision.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Acute liver failure (ALF)

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Gastroenterology

Internal Medicine

Intended Users

Advanced Practice Nurses

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To offer recommendations about controversial diagnostic and treatment strategies and predictive models for outcome in acute liver failure

Target Population

Adults ≥18 years of age with suspected or confirmed acute liver failure (ALF), defined as acute-onset liver disease with evidence of coagulopathy and/or hepatic encephalopathy without pre-existing liver disease

Interventions and Practices Considered

Diagnosis/Evaluation

Testing for Wilson's disease (not recommended routinely)

Testing for and treatment of herpes simplex virus (HSV)

Testing for varicella zoster virus (not recommended routinely)

Testing for hepatitis E virus in pregnant patients

Prognostic scoring systems (e.g., model for end-stage liver disease [MELD], Kings College Criteria)

Liver biopsy (not recommended routinely)

Autoantibody testing

<u>Treatment Management</u>

Empiric use of treatments to reduce intracranial pressure (ICP)

Extracorporeal artificial liver support systems (in a clinical trial)

N-acetyl cysteine for acetaminophen-associated acute liver failure only

Major Outcomes Considered

- Sensitivity and specificity
- Likelihood ratio (+/-)
- Transplantation and mortality
- All-cause mortality
- Transplant-free survival time
- Renal function
- Risk of infection
- Bleeding complications
- Electrolyte abnormalities
- Hepatic recovery
- N-acetyl cysteine (NAC) adverse events

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

<u>Defining the Clinical Questions</u>

Each statement followed the following format: population, intervention, comparator, and outcome (PICO). The population was adult acute liver failure (ALF) patients (age, >18 y) defined as acute-onset liver disease with evidence of coagulopathy and/or hepatic encephalopathy without pre-existing liver disease. The interventions were diagnostic tests such as tests for Wilson's disease; serology for herpes simplex, varicella zoster, or hepatitis E viruses; autoantibodies; prognostic scoring systems; liver biopsy; as well as therapeutic interventions such as N-acetyl cysteine, mannitol, barbiturates, hypothermia hyperventilation, hypertonic saline, lactulose, and artificial liver support systems. The comparator was usual care without the relevant diagnostic test or intervention and the main outcomes assessed were mortality, liver transplantation, and adverse events. For the diagnostic tests the reviewers sought information on diagnostic accuracy (sensitivity, specificity, and positive and negative likelihood ratios), but if this was not available they evaluated the prevalence of disease in the ALF populations. This was to provide evidence for the likely utility of a test as if the disease is very rare and there is no specific treatment then it may not be appropriate to test for this disease. A summary of the PICO questions is

given in Table 1 in the technical review document (see the "Availability of Companion Documents" field). The evidence and outcomes that were sought are outlined in Table 1, but in some cases this was not available and reviewers then evaluated indirect evidence to guide decision making. All PICO questions were investigated; when there was insufficient direct or indirect evidence to make any conclusions these questions were not included in the results.

<u>Identifying the Evidence</u>

The reviewers conducted an electronic search using MEDLINE, EMBASE, and the Cochrane Library until November 2015. An experienced information specialist developed search strategies for each statement. All authors iteratively refined the search strategy to maximize the sensitivity but not provide a prohibitively large number of titles (usually <1000 titles) to explore manually. The search was limited to the English language. Abstracts and letters were included but investigators did not explicitly search the grey literature for this evidence. The search strategies were developed to identify evidence for either a single statement or for 2 to 3 statements and these are outlined in Appendix 1 of the technical review (see the "Availability of Companion Documents" field).

When possible, the investigators used available systematic reviews to inform the clinical question and rated their validity according to commonly used criteria. Well-done systematic reviews that were missing recent trial data were updated and re-analyzed rather than creating a de novo systematic review. When well-done systematic reviews were unavailable, investigators searched for primary studies.

Therapeutic intervention evidence was restricted to randomized controlled studies, but observational studies were included for other statements. In the case of serology studies, single case reports were also evaluated. The investigators restricted searches to ALF in the adult population, but if data were limited they also evaluated the pediatric literature and patients with pre-existing liver disease as supportive information.

All titles were screened by one researcher and relevant articles were retrieved. A methodologist assessed eligibility for the technical review and another methodologist confirmed that articles were appropriate to include in an unblinded assessment.

Number of Source Documents

A total of 2320 references were identified in the search and 97 met inclusion criteria for the guideline technical review.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

<u>Grading of Recommendations Assessment, Development and Evaluation (GRADE) Definitions of Quality/Certainty of the Evidence</u>

High	The Committee is very confident that the true effect lies close to that of the estimate of the effect.
Moderate	The Committee is moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	The Committee's confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low	The Committee has very little confidence in the effect estimate. The true effect is likely to

Methods Used to Analyze the Evidence

Meta-Analysis

Meta-Analysis of Observational Trials

Meta-Analysis of Randomized Controlled Trials

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Well-done systematic reviews that were missing recent trial data were updated and re-analyzed rather than creating a de novo systematic review.

Synthesizing the Data

Randomized control trial data were summarized as relative risks (RR), whereas case–control studies were summarized using odds ratios (ORs), each with their 95% confidence intervals (CIs). Data were pooled using a random-effects model. Proportions were transformed using the Freeman–Tukey double-arcsine method, and then reviewers used an inverse-variance random-effects meta-analysis. Data on diagnostic accuracy were expressed as sensitivity and specificity as well as positive and negative likelihood ratios (LRs). A positive LR can be used to predict the probability of disease if the test is positive and a negative LR predicts the probability that the disease is absent if the test is negative. These measures are analogous to a positive and negative predictive value but have the advantage that they do not vary with the prevalence of disease. Where appropriate, data were pooled and summary receiver operator curves were constructed using hierarchical logistic regression. Positive and negative predictive values were calculated using LRs and applying the median absolute effect reported in the literature as well as plausible ranges from this value.

Assessing the Quality of Evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used for assessing quality of the evidence and this is graded as high, moderate, low, or very low (see the "Rating Scheme for the Strength of the Evidence" field). Randomized control trial (RCT) data are rated as high quality, but are rated down if one or more of the following are present: studies have a high risk of bias, are significantly inconsistent, provide imprecise estimates, or there is evidence of publication bias and/or indirectness, such as the evidence is not related directly to the population of interest. The more issues there are with the evidence from RCTs and the more severe the problem, the lower the quality of evidence is rated. Outcomes from observational studies start at low quality of evidence and can be rated down further if any of the issues described earlier are present. However, evidence can be rated higher if the effect is strong, there is a dose response, or any confounding would reduce the demonstrated effect. High-quality evidence suggests that the reviewers are confident of the direction and magnitude of the effect and any new data are unlikely to alter this.

Two methodologists evaluated the quality of the evidence according to these criteria for each statement and then discussed this with the team. All outcomes critical to decision making were evaluated, although frequently this was limited by the quantity and quality of the evidence. Reviewers intended to resolve any disagreements by consensus but there were no disagreements for this technical review. A summary of the quality of the evidence is given in Tables 2 and 3 and Supplementary Tables 1 and 2 of the technical review.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The American Gastroenterological Association Institute (AGA) process for developing clinical practice guidelines incorporates Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology and best practices as outlined by the Institute of Medicine. GRADE methodology was used to prepare the background information for the guideline and the technical review that accompanies it. Optimal understanding of this guideline will be enhanced by reading applicable portions of the technical review. The guideline panel and the authors of the technical review met face-to-face on May 20, 2016, to discuss the quality of evidence and consider other factors relevant for the risk-benefit assessment of the recommendations. The guideline authors subsequently formulated the recommendations. Although quality of evidence was a key factor in determining the strength of each recommendation, the panel also considered the balance between the benefit and harm of interventions, patients' values and preferences, and resource utilization.

Rating Scheme for the Strength of the Recommendations

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Categories on Strength of Recommendation

	Wording in Guideline	For the Patient	For the Clinician
Strong	"The AGA recommends..."	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.
Conditional	"The AGA suggests..."	The majority of individuals in this situation would want the suggested course of action, but many would not.	Different choices will be appropriate for different patients. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.

Cost Analysis

A cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This document presents the official recommendations of the American Gastroenterological Association Institute on initial testing and management of acute liver failure. The guideline was developed by the Clinical Guidelines Committee and approved by the American Gastroenterological Association Institute Governing Board.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

The recommendations included here represent a rigorous, evidence-based summary of extensive literature describing the diagnosis and treatment of acute liver failure (ALF) and use of predictive models. Review of this guideline, plus the associated technical review, will facilitate effective shared decision making with ALF patients.

See the original guideline document and the technical review (see the "Availability of Companion Documents" field) for information about potential benefits and the balance between the benefits and harms of specific interventions.

Potential Harms

- Six randomized controlled trials (RCTs) reported adverse events of extracorporeal liver support systems but data were presented in terms of individual events and could not be synthesized. Five RCTs reported that adverse events were very similar between the liver support systems and usual care with no statistically significant difference in any individual adverse event. One RCT stated that 2 of 12 patients randomized to Extracorporeal Liver Assist Device (ELAD) withdrew, 1 because of a fever and the other because of bleeding from the liver support site in the context of severe coagulopathy.
- One RCT did report on adverse events of N-acetyl cysteine (NAC) vs placebo and reported that nausea and vomiting occurred in 14% of NAC-treated patients compared with 4% treated with placebo (P = .03).

See the original guideline document and the technical review (see the "Availability of Companion Documents" field) for information about potential harms and the balance between the benefits and harms of specific interventions.

Qualifying Statements

Qualifying Statements

Limitations of Current Evidence and Future Directions

This technical review allows the clinician to better appreciate the nature of the data in important areas regarding acute liver failure. Current practice patterns may be based on evidence that is not robust and therefore does not inspire confident decision making for these very ill patients. This review, and the guideline that will be derived from it, can help guide the direction of further study in the areas of diagnosis, prognosis, and interventions in the management of the patient with acute liver failure. Data on the usefulness of diagnostic testing may allow more specific diagnosis, at less cost, than currently is

provided. An algorithmic approach to prognosis, which most likely will be based on MELD given the earlier data analysis, will provide the clinician with needed decision support. Finally, decisions regarding the use of expensive interventions such as artificial liver support, intracranial pressure monitoring, and liver transplantation should be scrutinized by the generation of higher-quality data.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Staff Training/Competency Material

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Flamm SL, Yang YX, Singh S, Falck-Ytter YT, AGA Institute Clinical Guidelines Committee. American Gastroenterological Association Institute guidelines for the diagnosis and management of acute liver failure. Gastroenterology. 2017 Feb;152(3):644-7. [4 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2017 Feb

Guideline Developer(s)

American Gastroenterological Association Institute - Medical Specialty Society

Source(s) of Funding

American Gastroenterological Association Institute

Guideline Committee

American Gastroenterological Association Institute Clinical Guidelines Committee

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Financial Disclosures/Conflicts of Interest

Conflicts of Interest

All members were required to complete a disclosure statement. These statements are maintained at the American Gastroenterological Association Institute headquarters in Bethesda, Maryland, and pertinent disclosures are published with the report.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Gastroenterology Journal Web site .

Availability of Companion Documents

The following are available:

Herrine SK, Moayyedi P, Brown RS Jr, Falck-Ytter YT. American Gastroenterology Association institute technical review on initial testing and management of acute liver disease. Gastroenterology. 2017 Feb;152(3):648–64. Available from the Gastroenterology Journal Web site _____.

Herrine SK, Moayyedi P, Brown RS Jr, Falck-Ytter YT. American Gastroenterology Association institute technical review on initial testing and management of acute liver disease. Online supplement. Appendix 1. Search strategies employed for the technical review. Gastroenterology. 2017 Feb. 5 p. Available from the Gastroenterology Journal Web site _____.

AGA process for developing guidelines. 2014 Dec. Available from the American Gastroenterological Association (AGA) Web site _____.

The AGA Institute process for developing clinical practice guidelines part one: grading the evidence. Clin Gastroenterol Hepatol. 2013 Apr;11(4):329-32. Available from the Clinical Gastroenterology and Hepatology Web site _____.

In addition, a continuing medical education activity is available from the Gastroenterology Journal Web site _____.

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on June 27, 2017. The information was verified by the guideline developer on August 24, 2017.

This NEATS assessment was completed by ECRI Institute on July 13, 2017. The information was verified by the guideline developer on August 24, 2017.

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